Complete Summary

GUIDELINE TITLE

Biochemotherapy for the treatment of metastatic malignant melanoma: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Verma S, Petrella T, Hamm C, Bak K, Charette M, Melanoma Disease Site Group. Biochemotherapy for the treatment of metastatic malignant melanoma: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2007 Apr 30. 25 p. (Evidence-based series; no. 8-3). [42 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Metastatic malignant melanoma

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Dermatology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the role of biochemotherapy in the treatment of metastatic malignant melanoma

TARGET POPULATION

Adult patients with metastatic malignant melanoma

INTERVENTIONS AND PRACTICES CONSIDERED

Biochemotherapy including:

1. Chemotherapy alone versus chemotherapy combined with interleukin-2 and interferon
2. Chemotherapy and interferon versus chemotherapy combined with interleukin-2 and interferon
3. Interferon and interleukin-2 with versus without chemotherapy

MAJOR OUTCOMES CONSIDERED

- Response rate
- Disease-free survival
- Overall survival
- Quality of life
- Incidence of grade 3 and 4 toxicities

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Literature Search Strategy

A systematic search of the following databases was undertaken: MEDLINE (1985 through April, week 3 2007), EMBASE (1980 to 2007 week 17), CANCERLIT (1985 through October 2002), the Cochrane Database of Systematic Reviews (2007, Issue 1), and the Cochrane Central Register of Controlled Trials (2007, Issue 2). The term "melanoma" (Medical subject heading (MeSH) and text word) was combined with variations of the terms "Interleukin-2" (MeSH and text word), "biochemotherapy" (text word) or "chemoimmunotherapy" (text word). These terms were then combined with the search terms for the following study designs: practice guidelines, systematic reviews, meta-analyses, randomized controlled trials or controlled clinical trials. In addition, the proceedings of the annual meetings of the American Society of Clinical Oncology for 1997 through 2006 were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guideline Clearinghouse (http://www.guideline.gov) were also searched for existing evidence-based practice guidelines. Relevant articles and abstracts were selected and reviewed by one member of the Melanoma Disease Site Group (DSG) and by two methodologists. The reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

Study Selection Criteria

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were:

1. Full reports or abstracts of randomized controlled trials in which one trial arm involved biochemotherapy for patients with metastatic malignant melanoma; or
2. Meta-analyses of randomized controlled trials, systematic reviews, or evidence-based practice guidelines.

Exclusion Criteria

1. Letters and editorials were not considered.
2. Papers published in a language other than English were not considered.
3. Reports that provided data for a sample of less than 10 patients with metastatic melanoma were not considered.
4. Phase II trials, including randomized trials, were not considered.

NUMBER OF SOURCE DOCUMENTS

Nine randomized controlled were included in this review

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

To estimate the overall effect of biochemotherapy on response, time-to-progression, and overall survival, data were abstracted from the published reports of individual randomized trials and pooled using the Review Manager software (RevMan 4.2) provided by the Cochrane Collaboration (Metaview © Update Software). For the pooled analysis of tumour response, the numbers of patients with a complete or partial response were abstracted from the text or tables in published reports. Time-to-progression and mortality data were obtained by estimating the number of patients who progressed or died within six and 12 months after randomization, from the Kaplan-Meier probability curves presented in each report. These numbers and the numbers randomized were used for the meta-analysis.

Results are expressed as relative risks (RR, also known as risk ratios) with 95% confidence intervals (CI). For tumour response, which represents a positive outcome, an RR>1.0 indicates that the patients in the experimental treatment group (biochemotherapy) experienced better response compared with those on the control treatment. For disease progression and mortality, which represent negative outcomes, an RR<1.0 indicates that the patients in the experimental treatment group (biochemotherapy) experienced delayed progression or fewer deaths compared with those on the control treatment. The random effects model was used for pooling across studies, in preference to the fixed effects model, as the more conservative estimate of effect.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Disease Site Group (DSG) Consensus

The draft guideline and systematic review were approved by the Melanoma Disease Site Group in December 2006. One member of the group suggested reversing the presentation of the data in one of the meta-analysis figures to provide a consistent direction of results, i.e., biochemotherapy benefit to the left and chemotherapy benefit to the right. However, since the data summarized in the figures represents a positive outcome in one analysis (tumour response) and a negative outcome in the other analyses (death or progression of disease), the current format of the analysis figures is consistent with the data, and the *Evidence Synthesis* section of the original report was revised to clarify this.

Report Approval Panel

Prior to submission of this evidence-based series report for external review, the report was reviewed and approved by the Program in Evidence-based Care (PEBC) Report Approval Panel in January 2007. The Panel consists of two members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Panel included whether the biochemotherapy regimens tested in the phase II trials that led to the reported phase III trials were consistent; if variation in response rates across the reported trials may be related to different tumour response evaluation criteria; the appropriateness of using 12-month mortality data for the meta-analysis when the report *Introduction* indicates that median survival for this patient group is six to eight months; and the inconsistency in the *Results* section of commenting on a survival trend in the Rosenberg trial, which suggests some benefit with chemotherapy, but not the Eton trial, which suggests some benefit with biochemotherapy. In addition, one member of the panel suggested it would be helpful to have explicit statements about "policy determining" outcomes. Since, in this case, the relevant outcomes appeared to be overall survival, coupled with treatment toxicity, a defining statement was suggested for the recommendation to indicate that.

The authors discussed the Report Approval Feedback and revised the report where appropriate. With regard to the treatment regimens used, an optimum regimen has not been identified for biochemotherapy and the regimens used in both phase II and phase III trials has varied, generally corresponding with specific institution or organization preferences. The criteria used to define a tumour response in most trials were that of the World Health Organization (or a similar definition) and a brief statement was added to the *Trial Descriptions* section of the *Systematic Review* to summarize that data. In considering the conduct of the meta-analysis, since the median survival for most of the reported trials was around 11-12 months; it was agreed that this was a reasonable time-point for data pooling. In addition, the six-month survival data were pooled with a similar result to that obtained at 12 months, and this was indicated in the *Results* section of the report. The need for consistency in presenting data was acknowledged and, following discussion of the results of the Rosenberg trial, a comment on the contrasting results of the Eton trial was added to the text of the *Results* section of the report. Finally, although the Program in Evidence-based Care guidelines are considered in policy determination, the authors consider their main purpose as providing guidance for clinicians and, therefore, do not wish to comment on policy-determining outcomes. In developing the recommendations, all relevant outcomes were considered, and it was felt that the current wording of the recommendation accurately reflects that fact; therefore, the recommendation was not revised.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

External Review by Ontario Health Care Providers

Following review and discussion of Sections 1 and 2 in the original guideline document of this evidence-based series report, and review and approval of the report by the Program in Evidence-based Care (PEBC) Report Approval Panel, the Melanoma Disease Site Group (DSG) circulated the draft report to health care providers in Ontario for review and feedback.

Methods

Feedback was obtained through a mailed survey of 12 medical oncologists in Ontario. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was mailed out on March 5, 2007. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Melanoma Disease Site Group reviewed the results of the survey.

This report reflects the integration of feedback obtained through the external review process with final approval given by the Melanoma DSG and the Report Approval Panel of the PEBC.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Due to the inconsistent results of the available studies with regard to benefit (response, time-to-progression, and survival) and consistently high toxicity rates, biochemotherapy is not recommended for the treatment of metastatic melanoma.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Seven of the nine trials reporting on response rate outcomes provided statistical comparisons. Only two trials reported statistically significant response rates favouring treatment with biochemotherapy, while five trials failed to detect any significant differences. None of the nine trials detected a statistically significant survival improvement with biochemotherapy.
- When data were pooled, biochemotherapy was superior to chemotherapy in terms of better response (relative risk, 1.52; 95% confidence interval, 1.24 to 1.87; p<0.0001) and delayed progression at six months (relative risk, 0.85; 95% confidence interval, 0.75 to 0.96; p=0.008) but not decreased mortality at 12 months (relative risk, 0.98; 95% confidence interval, 0.84 to 1.16; p=0.85).

POTENTIAL HARMS

Biochemotherapy is a toxic therapy, and patients are likely to experience serious hematologic, gastrointestinal, cutaneous, and constitutional toxicities. In addition, there are risks of cardiovascular toxicities such as myocardial events and arrhythmias, hypotension, capillary leak syndrome, hepatotoxicity, and renal toxicity. When conducted in the correct setting, grade 3 and 4 toxicities appear to be manageable, and treatment-related death can be minimized.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Verma S, Petrella T, Hamm C, Bak K, Charette M, Melanoma Disease Site Group. Biochemotherapy for the treatment of metastatic malignant melanoma: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2007 Apr 30. 25 p. (Evidence-based series; no. 8-3). [42 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2007 Apr 30

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Melanoma Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Melanoma Disease Site Group (DSG) disclosed information on potential conflicts of interest. No potential conflicts were declared.

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on Aug. 11, 2008. The information was verified by the guideline developer on August 25, 2008.

COPYRIGHT STATEMENT

DISCLAIMER

NGC DISCLAIMER

The National Guideline Clearinghouse™ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC

Inclusion Criteria which may be found at
http://www.guideline.gov/about/inclusion.aspx .

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.

Date Modified: 11/3/2008